Therapeutic and Aesthetic Uses of Photodynamic Therapy

Part four of a five-part series

ALA-PDT in Clinical Practice

How One Clinician Performs This Procedure

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ABSTRACT

The use of 5-aminolevulinic acid–photodynamic therapy in clinical practice is an individual determination based on experiences learned from clinicians and from personal experience. This manuscript reviews how one clinician approaches patients interested in having photodynamic therapy. It covers all practical aspects of the treatment process and reviews how photodynamic therapy can be utilized in your clinical practice. (*J Clin Aesthetic Derm.* 2009;2(1):32–35.)

This is the fourth article in a five-part series that examines photodynamic therapy (PDT) in the United States. In the previous installments, I have reviewed PDT and its effectiveness in treating actinic keratoses (AKs) and in photorejuvenation as well as its efficacy in the treatment of moderate-to-severe inflammatory acne vulgaris. I have also reviewed PDT's potential role as a chemopreventive agent in that it may be useful in preventing or delaying the onset of AKs and even nonmelanoma skin cancers in susceptible individuals, including immunosuppressed organ transplant patients. In this installment of the series, I examine how I utilize PDT in everyday practice. This is not a "scientific" article, *per se*, but more of a report on how PDT is used in my clinical practice, which has become standard among many dermatologists in the United States.

PDT is a process whereby a photosensitizer and light, in the presence of molecular oxygen, selectively destroys a targeted cell. In dermatology, 5-aminolevulinic acid (ALA) is the most common photosensitizer utilized in our clinics. The ALA currently available in the United States is known as Levulan® Kerastick™ (Dusa Pharmaceuticals, Wilmington, Massachusetts), and is shown in Figure 1. It is most commonly used with a blue light source. The most common blue light is known as the BluU® (Dusa Pharmaceuticals), shown in Figure 2. Levulan is a 20% 5-ALA solution and acts as a prodrug when applied to the skin where it is converted to its active form, protoporphyrin IX (PpIX). PpIX's absorption spectrum is shown in Figure 3. As seen in Figure 3, many lasers and light sources can be effective in activating PpIX, which has been demonstrated over the past several years.[1–3] The use of ALA-PDT has changed over the years (compared to its original "label" by the US Food and Drug Administration [FDA]), making it "easier" for physicians to utilize on a regular basis in their clinics. Most physicians now use "short-contact, full-face" application of ALA on the skin instead of the more constricting 14- to 18-hour drug incubation, as is written in the FDA approval.[4,5] The US Consensus Conference on the use of ALA–PDT confirmed this approach, as have many peer-reviewed clinical studies.[6]

A second photosensitizer, methyl ester of ALA (MAL), has recently been approved in the United States, although our experience with it is limited at the time of this writing. Known commonly as Metvixia® (PhotoCure ASA, Oslo, Norway; Galderma, Fort Worth, Texas) in the United States, it is best activated by the use of a red light source, the most common of which is known as the Aktilite® (PhotoCure ASA, Oslo, Norway; Galderma, Fort Worth, Texas) (Figures 4 and 5).

The US approval of Metvixia® is for the treatment of nonhyperkeratotic AKs of the face and scalp. In lesion preparation, a curette is used and then MAL is applied to the lesions, which are occluded for three hours and then

DISCLOSURE: Dr. Gold is a consultant to, speaks for, receives honoraria from, and owns stock in DUSA Pharmaceuticals; he is a Luminary for, speaks for, and owns stock in Lumenis; and is a consultant to and performs research for Galderma.

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subjected to the red light source. Clinicians recommend that two treatments of MAL be performed one week apart for maximum benefit.[7] Some of us are exploring the use of Metvixia® in our clinical practices and "experimenting" with various treatment protocols, including short-contact, full-face treatments to determine the optimum use of this product.

The remainder of this manuscript focuses on ALA-PDT, although many of the recommendations can be applied to MAL-PDT. Once again, please note that these are techniques employed in my clinical dermatology practice, and clinicians must decide what works best for their individual circumstances.

GETTING STARTED

The first discussion I always have with my patients is to review the risks and benefits associated with a PDT procedure. I explain every detail regarding the procedure, alternative therapies, and the benefits I hope to achieve through the use of ALA-PDT. I am always sure to document that risks and benefits of treatment were discussed with the patient. I also ensure that I receive a signed, written, informed consent of the procedure being performed from all of my patients. Remember that the FDA has approved ALA-PDT in the treatment of AKs, but has not approved it for photorejuvenation, acne vulgaris, and chemoprevention, which are considered off-label uses. Therefore, I thoroughly explain this to my patients as well.

Clinicians must take a thorough history of their patients to find out if they have any existing medical conditions. I do not know of any absolute contraindications to the use of ALA-PDT, although I would be cautious in patients with photosensitivity disorders, as photosensitivity is the major adverse event following the procedure. If a patient has a history of herpes simplex, I start him or her on an antiviral medication at least 2 to 3 days prior to the ALA-PDT procedure and continue the medication for several days after the procedure.

PREPARING THE SKIN

Before performing an ALA-PDT procedure, I thoroughly cleanse the patient's face with a mild cleanser. Then, I degrease the patient's skin to remove skin surface sebum and enhance the skin's absorption of ALA. The two most common methods to degrease the skin are microdermabrasion and/or aggressive acetone scrub. I routinely use an acetone scrub as it is less expensive than microdermabrasion. However, there is evidence that the use of microdermabrasion enhances the penetration of ALA.[8] Recent investigations have also shown that utilizing fractional resurfacing lasers enhances the penetration of ALA into the skin as well.[9,10] Both nonablative and ablative fractional devices can be used prior to application of ALA onto the skin.

APPLYING ALA TO THE SKIN

Next, I "break" the Levulan® Kerastick™ and mix it. The Kerastick™ is a 20% weight/volume ALA solution with 48% alcohol. It has a roll-on dermatologic applicator at one end

Figure 1. Levulan Kerastick (DUSA Pharmaceuticals, Wilmington, MA)

Figure 2. BluU blue light source (DUSA Pharmaceuticals, Wilmington, MA)

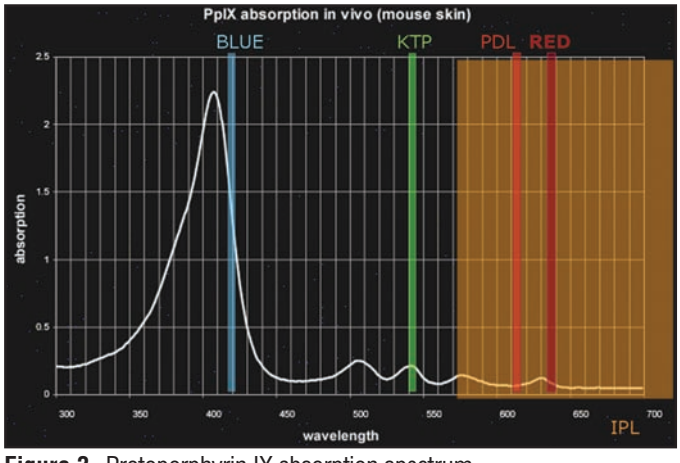

Figure 3. Protoporphyrin IX absorption spectrum

Figure 4. Metvix® (PhotoCure ASA, Norway; Galderma, Ft. Worth, Texas)

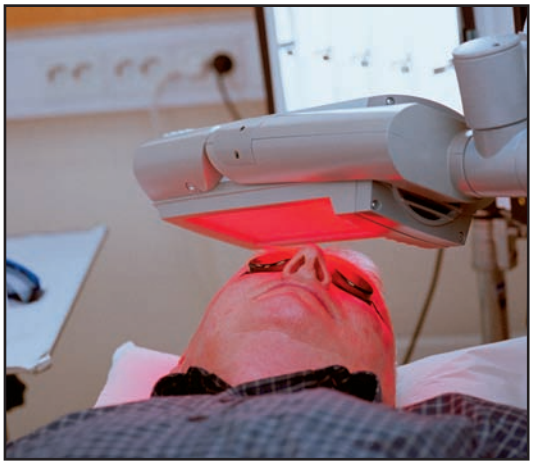

Figure 5. Red Light Source, Aktilite® (PhotoCure ASA, Norway; Galderma, Fort Worth, Texas)

to allow easy and accurate application of the medicine to the area(s) being treated. The applicator tip is connected to a flexible glass tubing that contains two glass vials. One of the vials contains ALA in a powder form; the other contains ethanol. Light manual pressure on pre-marked spots on the Kerastick™ (A and B) will break the vials allowing you to mix the two by gentle rotation in a back and forth direction. Three minutes of mixing is recommended prior to applying the medication to the treatment area.

As noted, most clinicians utilize a short-contact, full-face approach in the application of ALA-PDT. The ALA is "painted" onto the skin in a uniform manner covering the forehead, cheeks, chin, and nose area, followed by the scalp, if treating all of these areas. I apply the ALA in the same fashion for each treatment utilizing the cosmetic units as our guides. If a patient has hyperkeratotic AKs, I usually apply a second coat of ALA over the individual lesions. I then allow the drug to incubate on the skin surface. For all practical indications, drug incubation is from 30 minutes to one hour for photorejuvenation and AKs, 30 to 45 minutes for moderate-to-severe inflammatory acne vulgaris, and one hour for sebaceous gland hyperplasia. For each successive treatment, drug incubation may be increased by 15 to 30 minutes. Increasing drug incubation is determined by many factors, including the patient's response to the previous therapy, as well as taking into consideration any untoward effects from the therapy.

LASER OR LIGHT THERAPY

After the previously described steps have been taken, the patient is ready to have his or her laser or light treatment. I base this decision on many factors, including the indication for which I am treating and the type of laser or light source I have available in my clinic. Remember that only lasers and light sources that fit into the absorption spectrum of PpIX will work for PDT.

If an intense pulsed light (IPL) source is going to be used for the treatment, the skin must be cleansed again prior to the use of the light source to avoid the coupling gels from sliding off the skin. All of my treatments are carried out with the aid of additional cold air cooling by way of the Zimmer Cooler® (LaserMed, LLC, Shelton, Connecticut), which my patients hold and use as needed to cool the skin. Although cold air cooling appears useful for most patients, further research is needed to determine if it has any detrimental effects on PDT. Various manuscripts have reviewed the recommended settings for the various lasers and light sources used for PDT.[11–12] Keep in mind that many different devices can be used for PDT, and most physicians would recommend traditional photorejuvenation settings when utilizing these devices; there appears to be no need to decrease the fluences from these devices to affect the treatments as had originally been thought by some.

AFTER THE PROCEDURE

When the laser or light therapy is complete, I remove any remaining ALA on the surface of the skin. This can be accomplished by washing the skin thoroughly once again or by utilizing a five-minute, blue light "quenching" if either IPL or PDL are used, which is followed by skin washing. I apply ice to the treatment area after the procedure to alleviate any patient discomfort or skin burning.

Many reports of PDT address pain and discomfort during and following the procedure. We have all experienced this in our clinical practices, but I can assure you that, by using short-contact, full-face therapy, appropriate device settings, and proper cooling, most patients tolerate the procedure without any problems or concerns. Several articles have been published that try to compare pain from ALA and MAL. As clinicians, we must look at these carefully and note how long the drug incubations are and what kind of preparations of medicines are being used (brand versus compounded).[13–15] Most clinicians who utilize ALA-PDT in the manner I have described report very little discomfort or problems from the procedure.

The major adverse event from the procedure seems to be phototoxicity. I discuss the importance of remaining out of the sun for 24 to 48 hours after the procedure and tell my patients to wear sunscreen with a minimum SPF of

30. A zinc-oxide block can be beneficial as well. Several over-the-counter creams and lotions are available to help reduce post-treatment phototoxicity, and many are used routinely in offices in the United States.[16–18] I thoroughly explain to my patients that some erythema and desquamation are normal following the therapy; again this can be minimized by appropriate post-treatment care.

Patients also always ask how many treatments they will require for therapy to be successful. This is a difficult question to answer, and no clinical trials have been carried out to determine optimum treatment numbers. Most clinicians will use their clinical judgment to determine how many treatments one may need for the therapy to be successful. We can rely on the clinical trials already published as guides to explain to patients the proper number of treatments needed. I explain to my patients that for AKs and photorejuvenation, anywhere from 1 to 3 treatments on a monthly basis are usually required to achieve expected results; for acne vulgaris, I tell my patients to expect 2 to 4 treatments, and I try to do these every 2 to 3 weeks to achieve optimal results.

Proper post-therapy skin care is essential for all patients and is sometimes overlooked by clinicians not well versed in daily, routine, skin-care maintenance. There are a number of great skin care products on the market that have a positive effect on ALA-PDT treatments.

Finally, I want to address maintenance ALA-PDT treatments, which have also not yet been studied in clinical trials. A recent publication looking at long-term clearance of AKs showed that at 12 months the number of AKs expected in a group of AK patients is greatly reduced after ALA-PDT treatments.[19] Most of us utilizing ALA-PDT explain this maintenance concept to our patients and will treat patients several times a year to hopefully prevent new AKs from occurring. I do not always recommend maintenance for my acne patients, but I do tell them to return for further therapy if warranted.

The use of ALA-PDT, and soon MAL-PDT, has become routine in many dermatology offices. In my practice, we have become comfortable with the therapy and feel that our patients have benefited greatly from this therapy.

REFERENCES

1. Gold MH, Goldman MP. 5-Aminolevulinic acid photodynamic therapy: where we have been and where we are going. *Dermatol Surg.* 2004;30:1077–1084.
2. Gold MH. The evolving role of aminolevulinic acid hydrochloride with photodynamic therapy in photoaging. *Cutis*. 2002;69(6 Suppl):8–13.
3. Alexiades-Armenakas MR, Geronemus RG. Laser-mediated photodynamic therapy of actinic keratoses. *Arch Dermatol.* 2003;139(10):1313–1320.
4. Touma D, Yaar M, Whitehead S, et al. A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. *Arch Dermatol.* 2004;140(1):33–40.
5. Ruiz-Rodriguez R, Sanz-Sanchez T, Cordoba S. Photodynamic photorejuvenation. *Dermatol Surg.* 2002;28(8):742–724.
6. Nestor M, Gold MH, Kauvar A, et al. The use of photodynamic therapy in dermatology: results of a consensus conference. *J Drugs Dermatol.* 2006;5:140–154.
7. Pariser D, Loss R, Jarratt M, et al. Topical methyl-aminolevulinate photodynamic therapy using red light-emitting diode light for treatment of multiple actinic keratoses: a randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol.* 2008;59(4):569–576.
8. Fang JY, Lee WR, Shen SC, Fang YP, Hu CH. Enhancement of topical 5-aminolaevulinic acid delivery by Erbium:YAG laser and microdermabrasion: a comparison with iontophoresis and electroporation. *Br J Dermatol.* 2004;151(1):132–140.
9. Ruiz-Rodriguez R, López L, Candelas D, Zelickson B. Enhanced efficacy of photodynamic therapy after fractional resurfacing: fractional photodynamic rejuvenation. *J Drugs Dermatol.* 2007;6(8):818–820.
10. Gold MH. Fractionated aminolevulinic acid-photodynamic therapy provides additional evidence for the use of PDT for non-melanoma skin cancer [letter to the editor]. Accepted for publication. *J Eur Acad Dermatol Venereol.*
11. Gold MH. Aminolevulinic acid photodynamic therapy for actinic keratoses and photorejuvenation. *Expert Rev Dermatol.* 2007;2(4):391–402.
12. Gold MH. Aminolevulinic acid photodynamic therapy for cosmetic uses on the skin. *Giornale Italiano di Dermatologia e Venereologia.* 2007;142(4):311.
13. Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: a blinded, randomized, controlled trial. *Br J Dermatol.* 2006;154(5):969–976.
14. Kashe A, Luderschmidt S, Ring J, et al. Photodynamic therapy induces less pain in patients treated with methyl aminolaevulinate compared to aminolaevulinate acid. *J Drugs Dermatol.* 2006;5(4):353–356.
15. Gold MH. 5-Aminolevulinic acid photodynamic therapy versus methyl aminolevulinate photodynamic therapy for inflammatory acne vulgaris. *J Am Acad Dermatol.* 2008;58(2):S60–S62.
16. Gold MH, Biron JA. A novel skin cream containing a mixture of human growth factors and cytokines for the treatment of adverse events associated with photodynamic therapy. *J Drugs Dermatol.* 2006;5(8):796–798.
17. Gold MH. Single-center, split-face, double-blind, randomized clinical trial of the efficacy of a trolamine-containing topical emulsion and a topical petrolatum-based product in reducing redness and peeling after treatment with a microlaser peel. *Lasers Surg Med.* 2007;19:60.
18. Gold MH, Ribet V, Gral N, et al. Calming efficacy and tolerance of Avene Spring Water Gel after epilatory laser treatment combined to healing cream in adults. Poster presented at: 2006 American of Academy Dermatology Annual Meeting; San Francisco, CA.
19. Tschen EH, Wong DS, Pariser DM, et al. Photodynamic therapy using aminolevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp; phase IV multicentre clinical trial with 12-month follow-up. *Br J Dermatol.* 2006;155(6):1262–1269.